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Review

Biomarkers of disease activity in vitiligo: A systematic review☆,☆☆

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ABSTRACT

The pathophysiology of vitiligo is complex although recent research has discovered several markers which are linked to vitiligo and associated with disease activity. Besides providing insights into the driving mechanisms of vitiligo, these findings could reveal potential biomarkers. Activity markers can be used to monitor disease activity in clinical trials and may also be useful in daily practice. The aim of this systematic review was to document which factors have been associated with vitiligo activity in skin and blood. A second goal was to determine how well these factors are validated in terms of sensitivity and specificity as biomarkers to determine vitiligo activity. Both in skin (n = 43) as in blood (n = 66) an adequate number of studies fulfilled the predefined inclusion criteria. These studies used diverse methods and investigated a broad range of plausible biomarkers. Unfortunately, sensitivity and specificity analyses were scarce. In skin, simple histopathology with or without supplemental CD4 and CD8 stainings can still be considered as the gold standard, although more recently chemokine (C-X-C motif) ligand (CXCL) 9 and NLRP1 have demonstrated a good and possibly even better association with progressive disease. Regarding circulating biomarkers, cytokines (IL-1β, IL-17, IFN-γ, TGF-β), autoantibodies, oxidative stress markers, immune cells (Tregs), soluble CDs (sCD25, sCD27) and chemokines (CXCL9, CXCL10) are still competing. However, the two latter may be preferable as both chemokines and soluble CDs are easy to measure and the available studies display promising results. A large multicenter study could make more definitive statements regarding their sensitivity and specificity.

Contents

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1. Introduction

The pathophysiology of vitiligo is complex although the driving factors seem to become gradually elucidated. This may help to identify possible targets for treatment. In the coming years, new clinical trials are expected based on this scientific progress [1,2]. In this regard, a biomarker that allows an early and accurate determination of treatment response could be of considerable value. In contrast to other inflammatory skin disorders such as psoriasis or atopic dermatitis, vitiligo lacks obvious inflammatory signs, which can be easily evaluated by clinical examination. Several clinical activity signs have been described in vitiligo (such as hypochromic areas, blurred borders and confetti-like depigmentations, Koebners' phenomenon), although these signs are only present in a subset of active vitiligo patients [3]. Moreover, it is unclear whether these signs can be used to evaluate disease activity over time. The hallmark of vitiligo is its unpredictable clinical course, including periods of disease stability and disease flares. This complicates the daily management of vitiligo. Biomarker analysis could be useful to follow patients over time and even predict the chance of future disease progression, allowing to tailor the treatment to the individual biomarker profile.

The primary aim of this systematic review was to answer the following question: "Which factors have been linked to vitiligo activity in the skin and in the blood of vitiligo patients?". The secondary aim was to investigate the following question: "How well are these factors validated in terms of sensitivity/specificity to be used as a biomarker to determine disease activity?".

2. Methods

2.1. Search strategy, eligibility criteria and data extraction

A literature search was conducted using the PubMed and Embase database up to May 1st, 2017. All original research articles (including letters to the editor or correspondence) were included. Only studies that investigated non-segmental vitiligo patients were included, while studies investigating only segmental vitiligo patients were excluded. In studies investigating both non-segmental and segmental vitiligo patients, only the results of the non-segmental vitiligo patients were taken into account. There were no restrictions on the type of setting. All studies written in English, French or German listed in Medline through the Pubmed or Embase interface until May 1st, 2017 were considered (Fig. 1).

2.1.1. Part 1

Articles investigating the link between active vitiligo and histopathological characteristics/tissue expression were included. Studies that investigated a certain histopathological characteristic, the expression of an immunohistochemical staining, the expression of markers in tissue fluid or the quantitative expression of a gene with the purpose that this factor could be associated with active vitiligo were selected. Clinical disease activity was considered as the reporting of vitiligo progression in any form [Vitiligo Disease Activity (VIDA) scale, cut-off points…]. Studies that report no information on disease activity and miRNA studies were excluded. Only original research articles were included. Case reports ($n = 1$) were excluded. Furthermore, also studies that investigated a mixed population of active and stable patients without clarifying the results for both subgroups were excluded. Treatment induced disease stability was not considered as an adequate comparison as treatment might influence markers which are not necessarily related to disease activity.

The search strategy for Pubmed and Embase is listed as supplementary material. We extracted the investigated characteristic or factor (immunohistochemical staining, protein or gene expression), the tissue (lesional, perilesional, nonlesional), the number of patients/samples and the sensitivity or specificity to determine disease activity (if available). Markers associated with repigmentation were not taken into account.

2.1.2. Part 2

All circulating biomarkers linked to vitiligo activity were included. Studies that only investigated vitiligo patients versus controls without details on disease activity were excluded. There was no restriction on the method to stratify disease activity. Only publications that investigated an association between a circulating factor and disease activity were included. Genetic polymorphisms were not taken into account. Extracted data included were the investigated marker, the investigated sample types (serum, plasma), the number of patients/samples, information on the link with disease activity, the affected body surface area of the study population, results of the comparison of vitiligo patients with healthy controls and the sensitivity or specificity of the biomarker to determine disease activity (if available).

The search strategy used in Pubmed and Embase is listed as supplementary material.

2.2. Outcomes, data management, risk of bias and synthesis

The primary outcome was the association between a biomarker and vitiligo activity. The secondary outcome was the validation in terms of the number of studies, included patients and the reported sensitivity and specificity to confirm disease activity.

Literature search results were uploaded separately by 2 independent reviewers (RS and MS) through Zotero Software. This facilitated the comparison of included studies. The inclusion process was done as outlined in Fig. 1. In case of doubt or in the absence of an abstract, the full text was consulted. In case of discrepancy on the inclusion or exclusion of a study, this was in person discussed between RS, MS and NvG. Data were extracted by RS and verified by NvG. Publications were ordered according to the investigated factor (cytokine, chemokine…) and the concerned tissue (skin or blood). The author list and affiliated departments of the publications were screened for possible duplicate